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Brief Research Communication

No Association Between the Intronic Presenilin-1 Polymorphism and Alzheimer's Disease in Clinic and Population-Based Samples

Xingang Cai,[1] Judith Stanton,[1] Dani Fallin,[1] Jonathan Hoyne,[1] Ranjan Duara,[2] Michael Gold,[3] Steve Sevush,[4] Paul Scibelli,[1] Fiona Crawford,[1] and Michael Mullan[1]*

[1]*Roskamp Laboratories, Department of Psychiatry, University of South Florida, Tampa, Florida*
[2]*Mount Sinai Medical Center, University of Miami, Miami, Florida*
[3]*University of South Florida Memory Disorder Clinic, Tampa, Florida*
[4]*University of Miami Memory Disorder Clinic, Miami, Florida*

Mutations in the Presenilin 1 (PS1) gene on chromosome 14 cause most early-onset familial Alzheimer's disease (AD). An intronic polymorphism in the PS1 gene was recently identified and reported to be associated with late-onset AD [Wragg et al., Lancet 347: 509–512, 1996]. The authors found an excess of homozygotes for the more common allele (allele 1) in AD cases, associated with an approximate doubling of risk. In the present study, we report the PS1 polymorphism distributions in clinic and population-based samples. We were not able to replicate the findings of Wragg et al. [1996]. Our results are consistent with those of other researchers and do not support the conclusion that the PS1 polymorphism is associated with late-onset AD. Am. J. Med. Genet. 74:202–203, 1997. © 1997 Wiley-Liss, Inc.

KEY WORDS: Alzheimer's disease; psi gene; polymorphism

INTRODUCTION

Multiple exonic mutations in the Presenilin 1 (PS1) gene on chromosome 14 were recently linked to familial Alzheimer's disease (AD) with onset in the 40s [Sherrington et al. 1995]. Two other mutation-bearing genes (β-APP, PS2) also result in early-onset disease [Goate et al., 1991; Levy-Lahad et al., 1995]. These mutations are all very rare in contrast to the commonly occurring genetic variant of Apolipoprotein E allele 4 (APOE ε4) known to increase risk for AD in late-onset (above age 60) cases.

Wragg et al. [1996] recently reported an intronic polymorphism in the PS1 gene associated with late-onset AD. This clinic-based study found an increased risk for AD conferred by allele 1 of this polymorphism, specifically among homozygotes. We report neither genotypic nor allelic association for this polymorphism in either clinic or population-based AD samples with age-matched population-based controls, nor do we find any interaction of this polymorphism with APOE.

Late-onset clinic-based Alzheimer's cases in this study were self-referring to the University of South Florida and University of Miami Memory Disorder Clinics. Population memory disorder screens of aged individuals in the Miami/Dade County area provided AD cases as well as healthy control individuals above age 60. Those scoring poorly were subsequently evaluated and those diagnosed with Alzheimer's disease were included in this study. All cases met NINCDS-ADRDA criteria for probable or possible AD.

The 122 clinic and population AD samples and 256 population controls were genotyped at both the APOE and PS1 polymorphic sites according to previously published conditions and scoring methods [Wragg et al., 1996; Wenham et al., 1991]. The clinic-based and population-based data were then analyzed separately and together as shown in Table I. Chi-square and logistic regression analyses for both separate and combined data sets showed no significant association between any of the PS1 alleles or genotypes with AD diagnosis, while the well-known APOE ε4 risk association was seen in both populations (ε4 odds ratios: 2.9 [1.8–4.7], clinic; 4.1 [1.6–10.3], population; 3.08 [1.96–4.85], combined). Further regression analyses to detect any possible interaction between APOE genotypes and PS1 genotypes or allele doses were negative (data not shown).

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*Correspondence to: Dr. Michael Mulan, Roskamp Laboratories, Department of Psychiatry, University of South Florida, 3515 E. Fletcher Ave., Tampa, FL 33613.

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TABLE I. Allele and Genotype Frequencies and Chi-Square Analyses for Clinic and Population-Based Alzheimer's Cases and Population-Based Controls

	AD clinic	AD population	AD combined	Population controls	Odds ratio[a]
PS1 genotype	n = 102	n = 20	n = 122	n = 256	
1/1	32 (31.4%)	5 (25%)	37 (30.3%)	87 (34%)	0.83
1/2	57 (55.9%)	11 (55%)	68 (55.7%)	136 (53.1%)	0.97
2/2	13 (12.7%)	4 (20%)	17 (13.9%)	33 (12.9%)	1
	$P = .88$	$P = .573$	$\chi^2 = .513$, df = 2, $P = 0.774$		
PS1 alleles	n = 204	n = 40	n = 244	n = 512	
1	121 (59.3%)	21 (52.5%)	142 (58.2%)	310 (60.5%)	0.91
2	83 (40.7%)	19 (47.5%)	102 (41.8%)	202 (39.5%)	1
	$P > .05$	$P > .05$	$\chi^2 = .379$, df = 1, $P = 0.538$		

[a] Logistic regression for combined set.

In contrast to Wragg et al. [1996], none of the results presented here show association between AD and any of the PS1 polymorphism genotypes or alleles. Another group has found a significant excess of the 1/1 genotype in a clinic-derived Caucasian AD population with published controls and controls living in the vicinity of the clinic [Kehoe et al., 1996]. Fifty percent of the AD cases reported a family history of AD. A second group has made similar findings in a Japanese population of sporadic AD cases [Higuchi et al., 1996]. However, in another European population [Perez-Tur et al., 1996] and in a U.S. population of family history–negative AD cases and controls, neither genotypic nor allelic associations between the PS-1 polymorphism and AD were found [Scott et al., 1996a]. The U.S. authors suggested that the previous associations may be due to selection bias or to misuse of control data [Scott et al., 1996b]. In our data analysis, we are confident that a true association was not missed (no type II error), given that our combined set provided 90% power to detect a significant allele difference of at least 8.5% between groups, and a genotypic odds ratio of at least 2.08. The use of population-based cases and controls provides further confidence in our conclusion as we have previously shown that use of clinic derived samples (where family history status appears to be skewed) can greatly distort allelic frequencies and associations [Mullan et al., 1996]. It appears that similar biases may exist in the two Caucasian studies that report an association. Our data set does not appear to have such a distortion, as the APOE genetic profile and $\varepsilon 4$ risk association matches those of previously reported population samples [Mullan et al., 1996].

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